

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2005/000151

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K47/48		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61K C07K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, BIOSIS, EMBASE, BEILSTEIN Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NAKAMURA M ET AL: "Stereochemistry and Total Synthesis of Dolastatin E" TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 36, no. 28, 10 July 1995 (1995-07-10), pages 5059-5062, XP004027736 ISSN: 0040-4039 abstract page 5060 ----- -/--	1-27
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.		
<input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "Z" document member of the same patent family		
Date of the actual completion of the international search 23 February 2006		Date of mailing of the international search report 22. 06. 2006
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Dullaart, A

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>MCKEEVER B ET AL: "Total synthesis of the prenylated cyclopeptide trunkamide A, a cytotoxic metabolite from <i>Lissoclinum</i> sp" TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 42, no. 13, 26 March 2001 (2001-03-26), pages 2573-2577, XP004232300 ISSN: 0040-4039 p.2574, scheme1</p> <p>-----</p>	1-27
X	<p>LE H-T ET AL: "Design of potent dynorphin A-(1-9) analogues devoid of supraspinal motor effects in mice" CANADIAN JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY, vol. 75, no. 1, 1997, pages 9-14, XP008060098 ISSN: 0008-4212 abstract page 10, right-hand column, paragraph 3 - paragraph 4 page 11, right-hand column; table 2 page 12; table 3</p> <p>-----</p>	1-27
X	<p>CLAUSEN K ET AL: "STUDIES ON AMINO-ACIDS AND PEPTIDES 6. METHODS FOR INTRODUCING THIOAMIDE BONDS INTO THE PEPTIDE BACKBONE SYNTHESIS OF THE 4 MONOTHIO ANALOGS OF LEUCINE ENKEPHALIN" JOURNAL OF THE CHEMICAL SOCIETY PERKIN TRANSACTIONS I, no. 4, 1984, pages 785-798, XP002369346 ISSN: 0300-922X abstract page 785 table 1 page 788, scheme 2</p> <p>-----</p>	1-27
X	<p>LEHMANN J ET AL: "Synthesis of endothiopeptides and their cyclization to 1,3-thiazol- 5(4H)-imines" HELVETICA CHIMICA ACTA 1999 SWITZERLAND, vol. 82, no. 11, 1999, pages 1899-1915, XP002369347 ISSN: 0018-019X abstract figure 1 page 1904 - page 1906</p> <p>-----</p> <p style="text-align: center;">-/--</p>	1-27

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZACHARIE B ET AL: "Thioamides: Synthesis, stability, and immunological activities of thioanalogues of imreg. Preparation of new thioacylating agents using fluorobenzimidazolone derivatives" JOURNAL OF MEDICINAL CHEMISTRY, vol. 42, no. 11, 3 June 1999 (1999-06-03), pages 2046-2052, XP002369348 ISSN: 0022-2623 abstract page 2048, left-hand column, line 3 - page 2049, column I, line 8; compounds 8,11 -----	1-27
X	LAJOIE G ET AL: "FACILE REGIOSELECTIVE FORMATION OF THIO PEPTIDE LINKAGES FROM OLIGO PEPTIDES WITH NEW THIONATION REAGENTS" TETRAHEDRON LETTERS, vol. 24, no. 36, 1983, pages 3815-3818, XP002369349 ISSN: 0040-4039 the whole document -----	1-27
X	BROWN D W ET AL: "MONOTHIONOPEPTIDE AND DITHIONOPEPTIDE SYNTHESIS" TETRAHEDRON LETTERS, vol. 28, no. 19, 1987, pages 2171-2174, XP002369350 ISSN: 0040-4039 abstract page 2174 -----	1-27
X	ZACHARIE B ET AL: "Thioacylating agents. Use of thiobenzimidazolone derivatives for the preparation of thiotuftsins analogs" TETRAHEDRON, vol. 49, no. 46, 1993, pages 10489-10500, XP002369351 ISSN: 0040-4020 abstract page 10493 - page 10494 -----	1-27
X	LA COUR T F M: "STEREOCHEMISTRY OF PEPTIDES CONTAINING A THIOACYL GROUP" INTERNATIONAL JOURNAL OF PEPTIDE AND PROTEIN RESEARCH, vol. 30, no. 4, 1987, pages 564-571, XP008060097 ISSN: 0367-8377 page 567; table 1 ----- -/--	1-27

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ELMORE D T ET AL: "Thioesters of amino acid derivatives as thioacylating agents in thiopeptide synthesis" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, no. 5, May 1988 (1988-05), pages 1051-1055, XP002140044 ISSN: 0300-922X page 1053; table 3 -----	1-27
X	CAMPBELL P ET AL: "CARBOXYPEPTIDASE A CATALYZED HYDROLYSIS OF THIOPEPTIDE AND THIONESTER ANALOGUES OF SPECIFIC SUBSTRATES. AN EFFECT ON KAPPACAT FOR PEPTIDE, BUT NOT ESTER, SUBSTRATES" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 104, no. 19, 1982, pages 5221-5226, XP009029516 ISSN: 0002-7863 page 5222, left-hand column -----	1-27
X	LEHMANN J ET AL: "Site-Selective Incorporation of Thioamide-Linkages into a Growing Peptide" TETRAHEDRON, vol. 55, no. 17, 23 April 1999 (1999-04-23), pages 5359-5376, XP004223048 ISSN: 0040-4020 abstract schemes -----	1-27
X	SHAO Y ET AL: "Endothiopeptide inhibitors of HIV-1 protease" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 8, no. 6, 17 March 1998 (1998-03-17), pages 699-704, XP004136948 ISSN: 0960-894X abstract page 700 - page 701 table 1 -----	1-27
X	MCKEEVER B ET AL: "Total synthesis of trunkamide A, a novel thiazoline-based prenylated cyclopeptide metabolite from Lissoclinum sp" TETRAHEDRON, vol. 59, no. 15, 7 April 2003 (2003-04-07), pages 2713-2727, XP004417708 ISSN: 0040-4020 page 2714 -----	1-27
X	US 5 457 180 A (ZACHARIE ET AL) 10 October 1995 (1995-10-10) examples -----	1-27

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 91/01976 A (IAF BIOCHEM INTERNATIONAL INC) 21 February 1991 (1991-02-21) page 21, line 13 - page 23, line 12 examples -----	1-27
A	WO 99/20649 A (MERCK PATENT GMBH; NAUMANN, RENATE; JONCZYK, ALFRED; SCHMIDT, EVA-KATH) 29 April 1999 (1999-04-29) examples claims -----	1-27

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Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 38-39
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-27

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 38-39

Present claims 38 and 39 do not define the scope of protection sought in technical terms, contrary to the requirement of Article 6 PCT.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-27

A thiopeptide according to these claims

2. claims: 28-33,36-37

A drug conjugate according to these claims, and its use in a method of treatment.

3. claims: 34-35

An assay to detect transportation of a conjugate across a membrane.

INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5457180	A	10-10-1995	NONE	
WO 9101976	A	21-02-1991	AT 159521 T	15-11-1997
			AU 651557 B2	28-07-1994
			AU 6064290 A	11-03-1991
			CA 2059647 A1	05-02-1991
			DE 69031623 D1	27-11-1997
			DE 69031623 T2	19-02-1998
			DK 485458 T3	20-04-1998
			EP 0485458 A1	20-05-1992
			ES 2109236 T3	16-01-1998
			HU 63395 A2	30-08-1993
			JP 5501865 T	08-04-1993
			JP 3165698 B2	14-05-2001
			OA 9561 A	31-01-1993
			US 5138061 A	11-08-1992
			US 5371185 A	06-12-1994
WO 9920649	A	29-04-1999	JP 2001520236 T	30-10-2001